



Published in final edited form as:

Expert Opin Ther Targets. 2015 August ; 19(8): 1011–1015. doi:10.1517/14728222.2015.1044976.

The Potential of Sestrins as Therapeutic Targets for Diabetes

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Abstract

Sestrins (Sesn1/2/3) belong to a small protein family that has versatile biological functions. In addition to initially characterized oxidoreductase activity, sestrins also have oxidoreductase-independent functions, including activation of AMP-activated protein kinase (AMPK), inhibition of mechanistic target of rapamycin complex 1 (mTORC1), and activation of mTORC2. As these kinases are important for metabolic regulation, sestrins have a favorable profile as potential therapeutic targets for metabolic diseases such as diabetes. Recent data are in line with such a notion. In this editorial, I have attempted to provide some brief update on the major findings in regard to sestrins in metabolism.

Keywords

Akt; mTORC1; mTORC2; Sestrin

Sestrins – Regulators for AMPK and mTORC1

Sestrin proteins belong to a small family that is composed of three members (Sesn1/2/3) in mammals. The three sestrins share over 50% identical amino acid sequences throughout the entire proteins and ~70% in the carboxyl-terminal 145 amino acids (Figure 1). The amino acid sequences flanking the proposed catalytic cysteine (SESN1-C189, SESN2-C125, and SESN3-121) are completely identical among all three human sestrin proteins (Figure 1). By comparing with other proteins using a bioinformatics tool, the amino-terminal of the sestrin proteins share some similarity to a catalytic motif in prokaryotic proteins such as *Mycobacterium tuberculosis* AhpD, a component of alkyl-hydroperoxide reductase¹. Although sestrins have been shown to protect cells from oxidative stress, it is not clear whether the intrinsic enzymatic activity is required¹⁻³. However, more and more data suggest that sestrins have catalytic activity-independent functions. It has been reported that Sesn 1 and Sesn2 can activate AMP-activated protein kinase (AMPK) through a direct interaction with the α -subunits of the AMPK complex⁴. In the same study, Sesn1 and Sesn2 have also been shown to inhibit the activity of mechanistic target of rapamycin complex 1 (mTORC1), and the inhibition was proposed through the phosphorylation of tuberous sclerosis 2 (TSC2). Recently, it has been found that sestrins can modulate mTORC1 activity through at least two other mechanisms: 1) sestrins inhibit amino acid-induced RagA/B (Ras-related GTP binding A/B) guanine nucleotide exchange and mTORC1 translocation to the

lysosome⁵; 2) sestrins inhibit mTORC1 lysosomal translocation via interaction with the mTORC1 upstream regulator GATOR2 (GTPase-activating protein (GAP) activity toward Rags subcomplex2)^{6, 7} (Figure 2).

Since both AMPK and mTORC1 play critical roles in energy and nutrient homeostasis, as an upstream regulator of these two kinases, sestrins have been implicated in a number of biological processes (Figure 2). Sestrins have been shown to protect cells or organisms against oxidative stress through either their intrinsic enzymatic activity or a Nrf2 (also called Nfe2l2, nuclear factor erythroid 2-like 2)-mediated transcriptional response^{1, 2, 8}. Sestrins, especially Sesn2, are also protective against overnutrition-induced ER stress, possibly through inhibition of mTORC1⁹. Sestrins play a critical role in the activation of autophagy, an essential cellular maintenance process, through multiple mechanisms including activation of AMPK, inhibition of mTORC1, and activation of ULK1 (unc-51-like autophagy activating kinase 1) and sequestosome 1 (Sqstm1 or p62)^{2, 8, 10}. Furthermore, sestrins are also important regulators for metabolic homeostasis. Sesn2 and Sesn3 have been shown to suppress hepatic glucose production and promote glucose and lipid metabolism^{2, 8, 11-13}.

Sestrins– Remarkable Insulin Sensitizers

Recently, Sesn2 and Sesn3 have been shown to enhance insulin action in mouse models. Systemic deficiency of Sesn2 leads to worse glucose and insulin tolerance in high-fat-diet induced obese or genetic leptin-deficient ob/ob mouse models¹². It has been suggested that downregulated AMPK and overactivated mTORC1 might be responsible for the metabolic dysregulation when Sesn2 becomes deficient¹². In another study using liver-specific Sesn3 knockout and transgenic mouse models, it has been demonstrated that hepatic Sesn3 deficiency also causes insulin resistance and glucose intolerance under either regular chow or high-fat diet conditions¹³. Conversely, Hepatic Sesn3 overexpression improves insulin sensitivity and glucose homeostasis in transgenic mice under chow and high-fat diet conditions¹³. Intriguingly, AMPK does not seem to play a major role in the effects of Sesn3 on insulin sensitivity and glucose metabolism since hepatic Sesn3 overexpression in AMPK α 1/2 liver-specific double knockout mice shows the same effects as in the wild-type mice. Further biochemical analysis reveals a role of Sesn3 in the regulation of the mTORC2-Akt (also called PKB, protein kinase B) signaling¹³. The activation of Akt kinase requires two distinct phosphorylations – Thr308 and Ser473, catalyzed by two different kinases, Pdk1 (also called Pdk1, 3-phosphoinositide-dependent protein kinase 1) and mTORC2, respectively. Although it is not completely clear in molecular details, Sesn3 has been observed to interact with Rictor (rapamycin-insensitive companion of mTOR), an essential component of the mTORC2 complex. Such an interaction enhances the mTORC2 activity toward the Akt kinase¹³. Interestingly, Rosiglitazone, a peroxisome proliferator-activated receptor γ (PPAR γ) agonist and known insulin sensitizer, has been shown to upregulate Sesn1 in retinal cells¹⁴; however, it is not known whether the same effect occurs in other cell types. In addition, Sesn2 protein is stabilized by insulin in hepatocytes through the PI3K-mTORC1 pathway¹⁵. Intriguingly, acute Sesn2 knockdown also decreases phosphatase and tensin homolog (PTEN) and increases insulin signaling in hepatocytes¹⁵. However, chronic Sesn2 deficiency leads to insulin resistance in mice¹². How Sesn2 plays different roles under those conditions is not clear.

It can be envisioned that sestrin deficiency and/or functional impairment could lead to insulin resistance and metabolic disorders such as diabetes. Interestingly, three sestrin genes have different responses to overnutrition, *Sesn2* is induced by a high-fat diet in the liver and skeletal muscle of mice whereas *Sesn1* is decreased in the skeletal muscle and *Sesn3* is decreased in both the liver and adipose tissue but is increased in the skeletal muscle under the high-fat diet condition and the leg muscle biopsies of human diabetics^{12, 16}. To date, the major metabolic phenotypes from *Sesn2* and *Sesn3* knockout mice have been related to their hepatic functions. Thus, it has been proposed that sestrins could be the missing link in the selective hepatic insulin resistance whereby insulin continues to promote lipid biosynthesis but it is unable to suppress hepatic glucose production¹⁷. When the functions of sestrins are impaired, the mTORC1 activity is expected to increase and so is lipid and protein synthesis. At the same time, due to decreased activation of the mTORC2 complex by sestrins, Akt might not be sufficiently activated to control the activity of Foxos (forkhead box O) that are crucial transcription factors for hepatic gluconeogenesis. Therefore, hepatic glucose production is elevated under insulin resistance.

Conclusion

Sestrins play a critical role in metabolic control and glucose homeostasis through activation of AMPK and mTORC2 and inhibition of mTORC1. Therefore, *Sesn1/2/3* may represent a novel class of potential targets for therapeutic intervention of diabetes and metabolic syndrome.

Expert opinion

In my view, the research on sestrin biology has made remarkable progress in the last decade with a number of discoveries. First, sestrins are important defense factors against both endogenous and exogenous oxidative stress although the underlying mechanisms are incompletely understood. Second, sestrins can activate the key energy sensor AMPK and thus are critical for energy homeostasis. Third, sestrins inhibit mTORC1 translocation to the lysosome. This important regulation allows sestrins to modulate nutrient homeostasis, activate autophagy and suppress ER stress as well. Finally, sestrins can activate mTORC2 and thus sensitize insulin action. Overall, sestrins have salutary functions for metabolic homeostasis and hold exciting potentials for therapeutic applications including type 2 diabetes treatment.

Acknowledgments

This work was supported by the grant R01DK091592 (to X. C. D.) from the National Institute of Diabetes And Digestive And Kidney Diseases.

Annotated bibliography

*=of interest,

**=of considerable interest

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highlights box

- Sestrins are a rheostat for metabolic control.
- Sestrins activate the energy sensor AMPK during fasting.
- Sestrins suppress the mTORC1 activity during feeding.
- Sestrins sensitize insulin action via activation of the mTORC2 signaling.
- Sestrins control both glucose and lipid metabolism.

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SEN1 MAEGENEVRWDGLCSRSTTRETALENIRQTILRKTEYLRVSVKETPHRPSDGLSNTESD 60
SEN3 MNRGGG-----SPSAAANYLLCTN--- 19
SEN2 MIVADS-----ECRAELKDYLRFPAGG- 22
      * . . . : * :
SEN1 GLNKLHLHLLMSKRCPFKDVREKSEFILKSIQELGIRIPRPLGQGPSRFIPEKEILQVG 120
SEN3 -----CRKVLKDKR-----IRVSQPLTRGPSAFIPEKEVQAN 53
SEN2 -----VGDSGPGEQR-----ESRARRGPRGPSAFIPVEVLRG 57
      : : * : * : * : * : * : * :
SEN1 SEDAQMHALFADSFALGRDNLITLVMVFHPQYLESFLKTQHLLQMDGFLPLHYRHYIG 180
SEN3 TVDERTN-FLVEEYSTSGRLDNITQVMSLHTQYLESFLRSQFYMLRMDGFLPLPYRHYIA 112
SEN2 AESLEQH-LGLEALMSSGRVDNLAVVMGLHPDYFTSFWRLLHYLLHTDGLASSWRHYIA 116
      : . . . : * : * : * : * : * : * : * : * : * : * : * : * :
SEN1 IMAAARHQCSYLVNLHVNDLFHVGGDPKWLNGLENAPQKLQNLGELNKVLAHRPWLITKE 240
SEN3 IMAAARHQCSYLVNMHVDEFKLTGGIAEWLNGLEYVPQRLKNLNEINKLAHRPWLITKE 172
SEN2 IMAAARHQCSYLVGSHMAEFLQTGGDPEWLLGLHRAPEKLRKLSEINKLAHRPWLITKE 176
      ***** : * : * : * : * : * : * : * : * : * : * : * : * :
SEN1 HIEGLLKAEEHWSLAELVHAVVLLTHYHSLASFTFGCGISPEIHCDGGHTFRPPSVSNY 300
SEN3 HIQKLVKTGENNWSLPVLVHAVVLLAHYHALASFVFGSGINPERDPEISNGFRLISVNNF 232
SEN2 HIQALLKTGEHTWSLAELIQALVLLTHCHSLSSFVFGCGILPEGDADGSPAPQAPTTP- 234
      ** : * : * : * : * : * : * : * : * : * : * : * : * :
SEN1 CICDITNGNHSVDEMPVNSAENVSVSDSFFEVEALMEKMRQLQECRD-EEEASQEEMASR 359
SEN3 CVCDLANDNN--IENASLSGSNFGIVDSLSEALMERMKRLQEERE-DEEASQEEMSTR 289
SEN2 --SEQSSPPS-----RDPLNNSGGFESARDVEALMERMQQLQESLLRDEGTSQEEMESR 286
      : : . : * : * : * : * : * : * : * : * : * : * : * :
SEN1 FEIEKRESMFVFSDD-----DEEVTPARAVSRHFEDTSYGYKDFSRHG-MHVPTF 408
SEN3 FEKEKKESLFVVSQDTHFSFPHSDFEDDMIITSDVSRYIEDPGFGYEDFARRGEEHLPTF 349
SEN2 FELEKSESLLVTPSAD-----ILEPSPHDMLCFVEDPTFGYEDFTRRGAQAPPTF 337
      ** * * * : * . : : : : : : : : : : : : : : * * *
SEN1 RVQDYCWEDHGYSLVNRLYPDVGQLIDEKFHIAYNLTNTMAMHKDVDTSMLRRAIWNYYI 468
SEN3 RAQDYTWENHGFSLVNRLYSDIGHLLDEKFRMVYNLTNTMATHEDVDTMLRRAIFNYV 409
SEN2 RAQDYTWEDHGYSLIQRLYPEGGQLLDEKFQAAYSILTYNTIAMHSGVDTSVLRRRAIWNYYI 397
      * . * * * : * : * : * : * : * : * : * : * : * : * : * : * :
SEN1 HCMFGIRYDDYDYGEINQLLDRSFKVYIKTVVCTPEKVTKRMYSFWRQFKHSEKVVHNL 528
SEN3 HCMFGIRYDDYDYGEVNQLLERSLVYIKTVTCYPERTTKRMYSYWRQFKHSEKVVHNL 469
SEN2 HCVFGIRYDDYDYGEVNQLLERNLVYIKTVACYPEKTRRMYNLFWRHFRHSEKVVHNL 457
      ** : * * * * * : * : * : * : * : * : * : * : * : * :
SEN1 LLIEARMQAELLYALRAITRYMT 551
SEN3 LLMEARMQAELLYALRAITRHLT 492
SEN2 LLLLEARMQAALLYALRAITRYMT 480
      ** : * * * * * : * : * : * : * : * : * :

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Figure 1. Human sestrin proteins share high similarity in primary sequences

Human SESN1/2/3 protein sequences (Accession numbers: NP_055269, NP_113647, and NP_653266) were aligned using ClustalW2 program on the EMBL-EBI website. * indicates an identical amino acid among all three sestrins. The proposed catalytic cysteine residue is highlighted in a box.

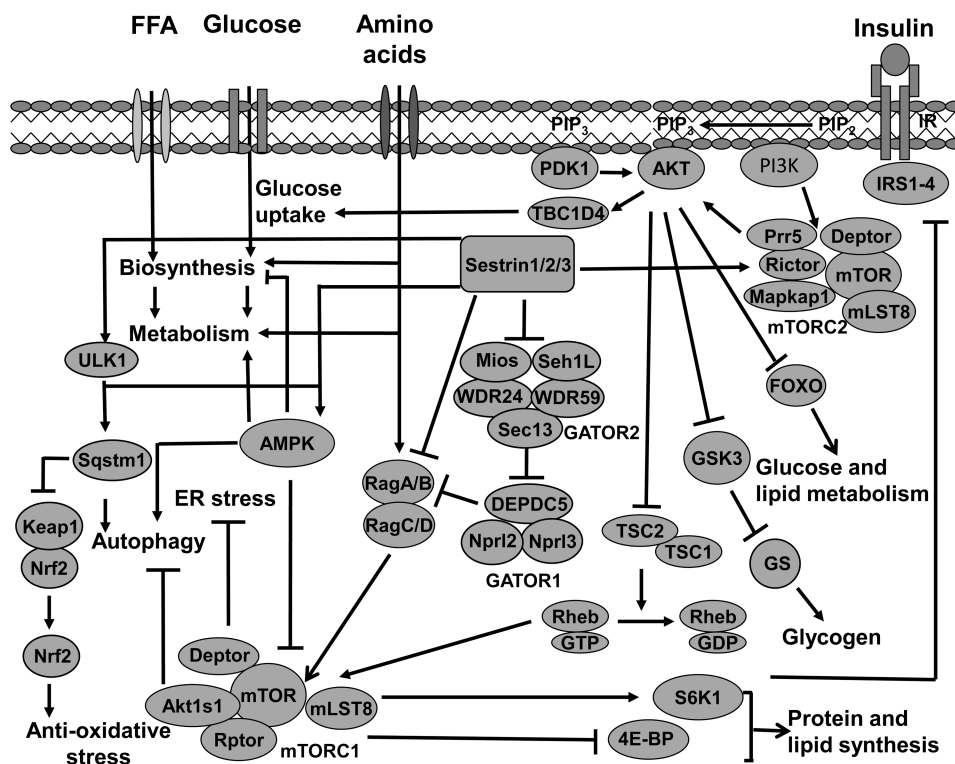


Figure 2. Signaling pathways regulated by sestrins in metabolism

Sestrins have been shown to regulate multiple signaling pathways that are important for metabolic homeostasis. Early on, AMPK was identified as a downstream kinase for the regulation of stress response to energy deprivation, reactive oxygen species, and genotoxins. It was also suggested that inhibition of mTORC1 by AMPK could play a critical role in those stress conditions. Later, it has been observed that sestrins can inhibit mTORC1 independently of AMPK, through either a direct inhibition of RagA/B GTPases or an indirect inhibition of RagA/B via GATOR2. Consequently, sestrins suppress the mTORC1 activity. Moreover, Sesn3 has been found to enhance insulin signaling through an activation of mTORC2. 4E-BP, eukaryotic translation initiation factor 4E binding protein 1; Akt, v-akt murine thymoma viral oncogene homolog; Akt1s1, Akt1 substrate 1; AMPK, AMP-activated protein kinase; DEPDC5, DEP domain containing 5; Deptor, DEP domain containing mTOR-interacting protein; ER, endoplasmic reticulum; FFA, free fatty acids; FOXO, forkhead box O; GATOR, GTPase-activating protein (GAP) activity toward Rags; GS, glycogen synthase; GSK3, glycogen synthase kinase 3; IR, insulin receptor; IRS, insulin receptor substrate; Keap1, kelch-like ECH-associated protein 1; Mapkap1, also called SIN1, mitogen-activated protein kinase associated protein 1; Mios, missing oocyte meiosis regulator homolog; mLST8, mTOR associated protein LST8 homolog; mTOR, mechanistic target of rapamycin; Nprl, nitrogen permease regulator-like; Nrf2, also called Nfe2l2, nuclear factor erythroid 2-like 2; PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Prr5, also called Protor 1, proline rich 5; Rag, Ras-related GTP binding; Raptor, also called Raptor, regulatory associated protein of mTORC1; Rheb, Ras homolog enriched in brain; Rictor, Raptor-independent companion of mTORC2; S6K1, also called RPS6KB1, ribosomal protein S6 kinase polypeptide 1; Sec13,

SEC13 homolog; Seh1L, SEH1-like; Sqstm1, sequestosome 1, also called p62; TBC1D4, TBC1 domain family member 4; TSC, tuberous sclerosis complex; ULK1, unc-51-like autophagy activating kinase 1; WDR, WD repeat domain.

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